REMARKS

Claim 64 has been amended in step (iv) to recite "determining whether the test compound modulates cellular growth or proliferation of the cancer cells in vitro." Support for this amendment may be found in the specification and claims as originally filed. No new matter has been added by way of amendment. Claims 64-72 will be pending upon entry of this amendment.

The Rejection of Claims 64-72 Under 35 USC §101 Should Be Withdrawn

The Examiner rejected claims 64-72 under 35 USC §101. The Examiner argued that the claimed invention is not supported by either a substantial utility or a well-established utility. Applicants respectfully traverse the rejection for reasons discussed below.

First, the Examiner stated:

> "Applicant argues that the specification at pages 10-12, Fig. 2 teach that the instantly claimed SE ID NO:2 is an acyl-coA dehydrogenase, and Zhang et al., (IDS, Biochem Biophys Res Commun., 2002 Oct 4;297(4):1033-42) at Fig. 5 teach that the protein (i.e. ACAD-9) identical to the instant SEQ ID NO:2 has dehydrogenase activity.
> These arguments have been fully considered but found unpersuasive. As shown in Fig. 5, the recombinant ACAD-9 protein catalyzes oxidation of stearoyl-CoA (C18:0) and palmitoyl-CoA (C16:0). But the recombinant ACAD-9 has little effect on *n*-octanoyl-CoA (C8:0), n-butyrl-CoA (C4:0) or isovaleryl CoA (C5:0);"

and,

> "The specific activity of the instant SEQ ID NO:2 is toward palmitoyl-CoA, with some activity also with stearoyl-CoA substrate. However, the instant specification does not teach that the instant SEQ ID NO:2 has dehydrogenase activity with palmitoyl-CoA or stearoyl-CoA."

Applicants assert that the specification does indeed teach that the DHDR-7 molecule of SEQ ID NO:2 is an acyl-CoA dehydrogenase. For example at page 7, lines 15-19, the specification teaches

> "The novel DHDR-7 molecules of the present invention are acyl-CoA dehydrogenases, which are mitochondrial flavoproteins that catalyze the alpha, beta-dehydrogenation of acyl-CoA esters and reduce an electron-transferring flavoprotein. This is the first step of

> the beta-oxidation cycle for fatty acids, which is a critical source of energy for the cell." (emphasis added)

Further, Applicants point out that such characterization of the enzyme of SEQ ID NO:2 is an acyl-CoA dehydrogenase is confirmed by Zhang et al., who teach ACAD-9, which is identical to instant SEQ ID NO:2, has acyl-CoA dehydrogenase activity. However, the Examiner appears to require not only teaching of "what kind(s) enzymatic reaction the protein carries out," but also delineation of the all of the specific substrates possibly metabolized by the protein. Applicants argue that such additional requirement is improper, and submit that one of ordinary skill in the art would recognize the utility of screening methods using the **acyl-CoA dehydrogenase** of instant SEQ ID NO:2, based on the definition of the molecule as an acyl-CoA dehydrogenase enzyme as discussed herein and its differential expression in various tumors as compared to their respective normal tissues.

Next, the Examiner stated:

> "Applicant argues that the specification at Tables 1-2 (pages 86-90) teach that the nucleic acid encoding the claimed dehydrogenase is differentially expressed in various tumors, therefore the product is [a] good target for cancer therapy.
> However, Zhang et al., (IDA) teach that Northern blot analysis showed a transcript of ~2.6 kb of ACAD-9 ubiquitously expressed in most normal tissues with high expression in heart, skeletal muscles, brain, kidney, and liver. "

Applicants do not dispute the expression data of Zhang et al. Rather, Applicants respectfully point out that the expression data presented in the instant specification is differential expression data. In other words, the data presented are of expression in a disease tissue (e.g. lung tumor cells) relative to the normal tissue (e.g. normal lung cells). For example, the specification at Table 1 (please see page 87), teaches increased expression in 4/4 lung tumor cells compared to 0/2 normal lung cells as determined by in situ hybridization. In addition, Table 2 of the specification (please see page 89) shows increased relative expression in a variety of lung tumors (Lung T) versus normal lung tissue (Lung N) as determined by quantitative RT-PCR. Thus, the instant expression data would indicate to one of skill in the art that a difference in expression exists between normal tissues and tumors of those tissues, as described in the specification. Zhang et al. do not disclose any expression data pertaining to the expression of ACAD-9 in diseased tissues on their own or relative to normal tissues. Therefore, the two sets of data are not inconsistent.

In addition, the Examiner stated:

> "As stated in the previous Office action, the specification fails to teach what kind(s) enzymatic reaction the protein carries out. In other words, the specification fails to teach the substrate of the instant SEQ ID NO:2 as taught by the post-filing publication of Zhang et al."

As stated above, Applicants submit that the specification does indeed teach what kind of enzymatic reaction the molecules of the invention carry out, namely that they are "acyl-CoA dehydrogenases, which are mitochondrial flavoproteins that catalyze the alpha, beta-dehydrogenation of acyl-CoA esters and reduce an electron-transferring flavoprotein." (please see page 7, lines 15-17; emphasis added). Applicants submit that one of skill in the art at the time of filing could have screened a panel of potential substrates, as Zhang et al. had, to find one substrate out of potentially many to use in the claimed screening method, and that this would not require undue experimentation. Therefore, the recitation of a specific substrate would not have been necessary for one of skill in the art to make and use the claimed method, and would instead perhaps be unnecessarily restrictive as to which substrates could be used for the screening method.

In addition, Applicants argue that the Examiner's argument using the references of Scott et al., Skolnick et al., Bork et al., Doerks et al., Smith et al., Brenner et al., and Bowie et al., which purportedly describe the difficulty in predicting function based on structural similarity to known proteins, does not apply to the instant case, as the studies of Zhang et al. and others have confirmed that the protein of SEQ ID NO:2 shows the enzymatic activity asserted in the specification, and is indeed an acyl-CoA dehydrogenase. So, in this case, the argument using Scott et al., Skolnick et al., Bork et al., Doerks et al., Smith et al., Brenner et al., and Bowie et al., does not apply.

The Examiner also took the position that:

> "Furthermore, the specification does not teach a relationship to any specific disease or establish any involvement SEQ ID NO:2 protein in the etiology of any specific disease. The specification does not teach a relationship between the different tissue distribution of the protein to any specific disease or etiology of any specific disease, either."

Applicants submit that, contrary to the Examiner's assertion, the specification does indeed teach a relationship to a specific disease, and does indeed teach a relationship between the tissue distribution of the DHDR-7 molecules and a specific disease. In fact, this specific disease is cancer, including but not limited to lung cancer, colon cancer, breast cancer, and ovarian cancer, as described in the specification. For example, the specification at page 7, lines 19-26, teaches:

> "Rapidly growing and dividing tumor cells have increased energy requirements. Increased expression of DHDR-7 in tumor cells contributes to increased energy production, and increased energy production contributes to cellular growth and proliferation, thereby increasing tumorigenesis and metastasis of tumor cells, *e.g.*, colon tumor cells, breast cancer tumor cells, lung tumor cells, and ovarian tumor cells. Accordingly, the DHDR-7 molecules of the present invention provide novel diagnostic targets and therapeutic agents to control cellular growth or proliferation disorders, *e.g.*, cancer, including, but not limited to, colon cancer, breast cancer, lung cancer, and ovarian cancer."

Furthermore, as discussed above, the specification teaches differential expression of DHDR-7 in, for example, lung cancer (please see, for example, Table 1 on page 87, and Table 2 on page 89). Thus, the specification does teach a relationship to a specific disease, and it also teaches differential expression in tumors versus normal tissue for a variety of tissue types.

The Examiner additionally argued that:

> "As for the second part of the claimed method, i.e. to determine whether the prescreened SEQ ID NO:2 binding compounds a cytotoxic effect to cancer cells in vitro is not considered to be specific, substantial and credible, for the following reasons: the implicit assertion of anticancer activity for the protein is not substantial;"

The Examiner cited Johnson et al. (Brit . J. Cancer 84(10):1424-1431) as stating that

> "Agents selected on the basis of potency, selective activity against a particular disease category, and/or differential activity against a few specific cell lines were then evaluated against a small number of sensitive human tumours in the nude mouse xenograft model (citations omitted) as a basis for selecting compounds for further preclinical development."

and then stated,

> "Thus, the initial screen... is not considered by the art to be predictive of in vivo activity against tumors, and, as characterized by Johnson et al., such is merely the first of a three-part protocol for identification of agents to be tested in vivo."

The Examiner also cited Shi et al., (J. Chem. Inf. Comput. Sci. 40:367-379), saying that it

> "states that relative activity levels distinguish better among the tested cell lines than do the GI_{50} activity patterns...Thus, Shi et al indicates that the art does not

> consider the raw GI_{50} data [sufficient] to identify compounds that are likely to be antitumor candidates to be tested further."

and further argued,

> "The instant claims are drawn to use of SEQ ID NO:2, which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the SEQ ID NO:2 protein used in the claimed screening assay is incomplete."

In citing Johnson et al. and Shi et al., the Examiner appears to assert that the claimed method requires additional steps where the effect of a candidate compound *in vivo* is determined. Applicants submit that the claimed method is directed to identifying a candidate compound capable of modulating cellular growth and/or proliferation of cancer cells *in vitro*. Furthermore, Applicants have amended step (iv) of claim 64 to recite that this determining step occurs *in vitro*. Thus, Applicants submit that the rejection in this respect is rendered moot by this amendment. If the Examiner is minded to maintain the rejection in this respect, Applicants respectfully request clarification.

Also, as discussed above, the DHDR-7 molecules of the instant invention do indeed have specific function and biological significance: the specification teaches that DHDR-7 is an acyl-CoA dehydrogenase which catalyzes the alpha, beta dehydrogenation of an acyl-CoA ester; and DHDR-7 is differentially expressed in a variety of tumors compared to their respective normal tissues (by two methods) (please see above).

Applicants submit that a credible, specific and substantial utility has been properly asserted in the specification as filed. Therefore, Applicants respectfully believe the Examiner's imposition of the present rejection is improper, and as such the rejection under 35 USC §101 should be withdrawn. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 64-72 under 35 USC §101.

The Rejection of Claims 64-72 Under 35 USC §112, First Paragraph (Enablement) Should Be Withdrawn

Claims 64-72 were rejected under 35 USC §112, first paragraph due to lack of satisfying the utility requirement. For the reasons discussed above, Applicants submit the utility requirement has been met and as such, one of skill in the art would know how to use the invention. Applicants therefore respectfully request reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph.

CONCLUSIONS

In view of the remarks and amendment made herein, Applicants respectfully submit that the rejections presented by the Examiner are now overcome and that this application is in condition for allowance. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

This paper is being filed timely as a request for a three month extension of time is filed concurrently herewith. No additional extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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